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(71) Demandeur/Applicant:
GRUENENTHAL GMBH, DE

(72) Inventeurs/Inventors:
ARKENAU-MARIC, ELISABETH, DE;
BARTHOLOMAEUS, JOHANNES, DE

(74) Agent: FETHERSTONHAUGH & CO.

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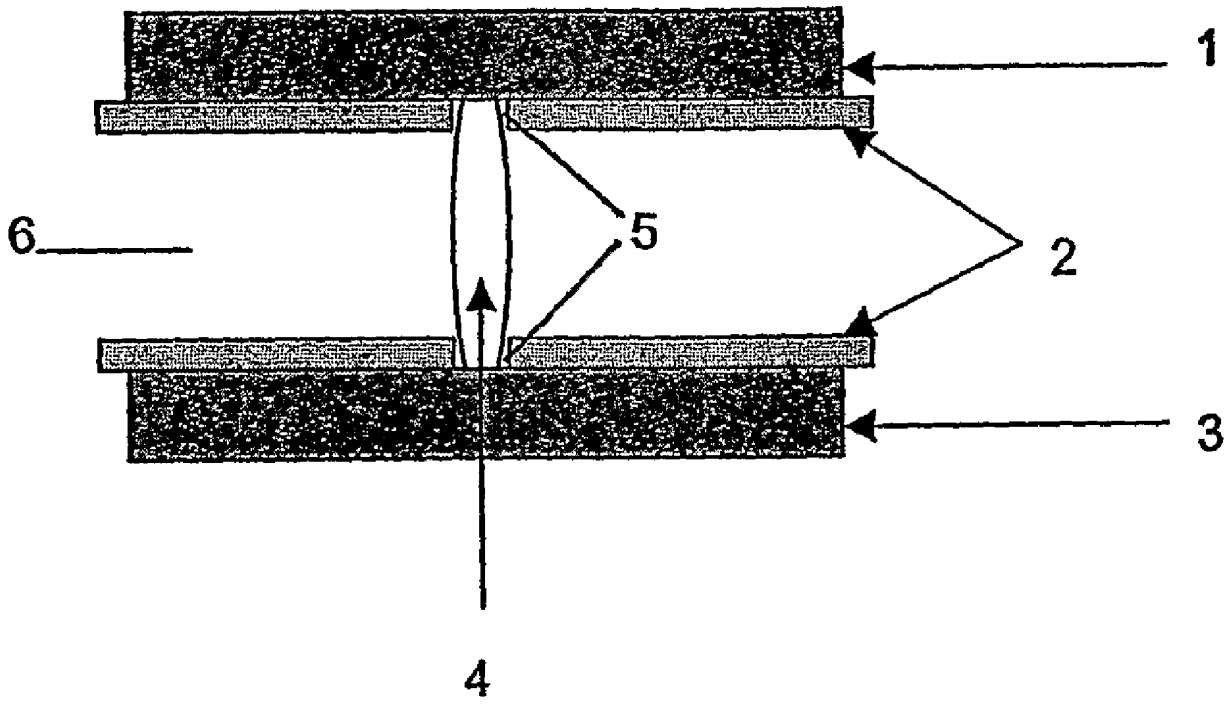
(54) Title: METHOD FOR THE PRODUCTION OF A TAMPER-PROOF FORM OF ADMINISTRATION



(57) Abrégé/Abstract:
The invention relates to a method for producing a tamper-proof form of administration containing at least one synthetic or natural polymer (C) having a minimum breaking strength of 500 N in addition to one or several tamper-prone agents and optional physiologically acceptable adjuvants. A solvent for the polymer (C) is added to the formulation mixture at such amounts that the formulation mixture is at least evenly moistened, the at least moistened mass is optionally subdivided into partial masses, is dried, and is shaped into the form of administration.

ABSTRACT

The invention relates to a method for producing a tamper-proof form of administration containing at least one synthetic or natural polymer (C) having a minimum breaking strength of 500 N in addition to one or several tamper-prone agents and optional physiologically acceptable adjuvants. A solvent for the polymer (C) is added to the formulation mixture at such amounts that the formulation mixture is at least evenly moistened, the at least moistened mass is optionally subdivided into partial masses, is dried, and is shaped into the form of administration.

Process for the production of an abuse-proofed dosage form

The present invention relates to a process for the production of an abuse-proofed solid dosage form, in which there is added to a formulation mixture containing, apart from one or more active ingredients with potential for abuse (A) and optionally physiologically acceptable auxiliary substances (B) and at least one synthetic or natural polymer (C), which exhibits a breaking strength of at least 500 N,

a) a solvent for the polymer (C) at least in quantities such that the formulation mixture is uniformly moistened,
b) the composition which has been at least moistened in this manner is optionally divided into sub-portions,
c) the portion(s) are dried and
d) shaped to yield the dosage form

Many pharmaceutical active ingredients, in addition to having excellent activity in their appropriate application, also have potential for abuse, i.e. they can be used by an abuser to bring about effects other than those intended.
Opiates, for example, which are highly active in combating severe to very severe pain, are frequently used by abusers to induce a state of narcosis or euphoria.

In order to make abuse possible, the corresponding dosage forms, such as tablets or capsules are comminuted, for example ground in a mortar, by the abuser, the active ingredient is extracted from the resultant powder using a preferably aqueous liquid and the resultant solution, optionally after being filtered through cotton wool or cellulose wadding, is administered parenterally, in particular intravenously. An additional phenomenon of this kind of administration, in comparison with abusive oral administration, is a further accelerated increase in active ingredient levels giving the abuser the desired effect, namely the "kick" or "rush". This kick is also obtained if the powdered dosage form is administered nasally, i.e. is sniffed.

Since delayed-release oral dosage forms containing active ingredients with potential for abuse conventionally do not give rise to the kick desired by the abuser even when taken orally in abusively high quantities, such dosage forms are also comminuted and extracted.

US-A-4,070,494 proposed adding a swellable agent to the dosage form in order to prevent abuse. When water is added to extract the active ingredient, this agent swells and ensures that the filtrate separated from the gel contains only a small quantity of active ingredient.

The multilayer tablet disclosed in WO 95/20947 is based on a similar approach to preventing parenteral abuse, said tablet containing the active ingredient with potential for abuse and at least one gel former, each in different layers.

WO 03/015531 A2 discloses another approach to preventing parenteral abuse. A dosage form containing an analgesic opioid and a dye as an aversive agent is described therein. The colour released by tampering with the dosage form is intended to discourage the abuser from using the dosage form which has been tampered with.

Another known option for complicating abuse involves adding antagonists to the active ingredients to the dosage form, for example naloxone or naltexone in the case of opioids, or compounds which cause a physiological defence response, such as for example ipecacuanha (ipecac) root.

Since, however, as in the past, it is in most cases necessary for the purposes of abuse to pulverise the dosage form, it was the object of the present invention to provide a process for the production of dosage forms containing active ingredients with potential for abuse, which, when correctly administered, ensure the desired, preferably therapeutic action, but from which the active ingredients cannot be converted into a form suitable for abuse simply by pulverisation.

Said object has been achieved by the provision of the process according to the invention for the production of a solid dosage form with at least reduced potential for abuse which is characterised in that

a) there is added to a formulation mixture containing at least one active ingredient with potential for abuse (A) and at least one synthetic or natural polymer (C), which exhibits a breaking strength of at least 500 N, a solvent for the polymer (C) at least in quantities such that the formulation mixture is uniformly moistened
b) the composition which has been at least moistened in this manner is optionally divided into sub-portions,
c) the portion(s) are dried and
d) shaped to yield the dosage form.

By using polymers having the stated minimum breaking strength (measured as stated in the application), preferably in quantities such that the dosage form also exhibits such a minimum breaking strength of at least 500 N, preferably of at least 1000 N, it is possible to prevent pulverisation of the dosage form with conventional means and thus considerably to complicate or to prevent any subsequent abuse.

If comminution is inadequate, parenteral, in particular intravenous, administration cannot actually be performed safely or extraction of the active ingredient therefrom takes too long for the abuser or there is no "kick" when orally abused as release is not instantaneous.

According to the invention, comminution is taken to mean pulverisation of the dosage form by the application of force with conventional means which are conventionally available to an abuser, such as for example a pestle and mortar, a hammer, a mallet or other usual means for pulverisation, wherein the proportion of fines which may arise (particle size equal to or smaller than 0.3 mm) must not exceed 5 wt.%.

The dosage form produced according to the invention also cannot be comminuted by these methods at low temperatures, for example of below –25°C, -40°C or even in liquid nitrogen.

The dosage form produced according to the invention, preferably a pharmaceutical dosage form, is thus suitable for preventing parenteral, nasal and/or oral abuse of active ingredients, preferably of pharmaceutical active ingredients, with potential for abuse.

Active ingredients, preferably pharmaceutical active ingredients with potential for abuse are known to the person skilled in the art, as are the quantities thereof to be used and processes for the production thereof, and may be present in the dosage form produced according to the invention as such, in the form of the corresponding derivatives thereof, in particular esters, ethers or amides, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the corresponding salts or solvates thereof, as racemates or stereoisomers. The dosage form produced according to the invention may contain two or more pharmaceutical active ingredients. The dosage form produced according to the invention preferably contains only one specific active ingredient.

The dosage form according to the invention is in particular suitable for preventing the abuse of at least one pharmaceutical active ingredient, which is selected from the group comprising opioids, tranquillisers, preferably benzodiazepines, barbiturates, stimulants and further narcotics.

The dosage form according to the invention is very particularly suitable for preventing abuse of an opioid, tranquilliser or another narcotic selected from the group comprising N-{1-[2-(4-ethyl-5-oxo-2-tetrazolin-1-yl)ethyl]-4-methoxymethyl-4-piperidyl}propionanilide (alfentanil), 5,5-diallylbarbituric acid (allobarbital), allylprodine, alphaprodine, 8-chloro-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-a][1,4]-benzodiazepine (alprazolam), 2-diethylaminopropiophenone (amfepramone), (±)-α-methylphenethylamine (amphetamine), 2-(α-methylphenethylamino)-2-phenylacetonitrile (amphetaminil), 5-ethyl-5-isopentylbarbituric acid (amobarbital), anileridine, apocodeine, 5,5-diethylbarbituric acid (barbital), benzylmorphine, bezitramide, 7-bromo-5-(2-pyridyl)-1*H*-1,4-benzodiazepine-2(3*H*)-one (bromazepam), 2-bromo-4-(2-chlorophenyl)-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-a][1,4]diazepine (brotizolam), 17-cyclopropylmethyl-4,5α-epoxy-7α[(S)-1-hydroxy-1,2,2-trimethyl-propyl]-6-methoxy-6,14-*endo*-ethanomorphinan-3-ol (buprenorphine), 5-butyl-5-ethylbarbituric acid (butobarbital), butorphanol, (7-chloro-1,3-dihydro-1-methyl-2-oxo-5-phenyl-2*H*-1,4-benzodiazepin-3-yl) dimethylcarbamate (camazepam), (1*S*,2*S*)-2-amino-1-phenyl-1-propanol (cathine/D-norpseudoephedrine), 7-chloro-*N*-methyl-5-phenyl-3*H*-1,4-benzodiazepin-2-ylamine 4-oxide (chlordiazepoxide), 7-chloro-1-methyl-5-phenyl-1*H*-1,5-benzodiazepine-2,4(3*H*,5*H*)-dione (clobazam), 5-(2-chlorophenyl)-7-nitro-1*H*-1,4-benzodiazepin-2(3*H*)-one (clonazepam), clonitazene, 7-chloro-2,3-dihydro-2-oxo-5-phenyl-

1*H*-1,4-benzodiazepine-3-carboxylic acid (clorazepate), 5-(2-chlorophenyl)-7-ethyl-1-methyl-1*H*-thieno[2,3-e][1,4]diazepin-2(3*H*)-one (clotiazepam), 10-chloro-11b-(2-chlorophenyl)-2,3,7,11b-tetrahydrooxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one (cloxazolam), (-)-methyl-[3β-benzoyloxy-2β(1αH,5α*H*)-tropane carboxylate] (cocaine), 4,5α-epoxy-3-methoxy-17-methyl-7-morphinen-6α-ol (codeine), 5-(1-cyclohexenyl)-5-ethyl barbituric acid (cyclobarbital), cyclorphan, cyprenorphine, 7-chloro-5-(2-chlorophenyl)-1*H*-1,4-benzodiazepin-2(3*H*)-one (delorazepam), desomorphine, dextromoramide, (+)-(1-benzyl-3-dimethylamino-2-methyl-1-phenylpropyl)propionate (dextropropoxyphene), dezocine, diampromide, diamorphone, 7-chloro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (diazepam), 4,5α-epoxy-3-methoxy-17-methyl-6α-morphinanol (dihydrocodeine), 4,5α-epoxy-17-methyl-3,6a-morphinandiol (dihydromorphine), dimenoxadol, dimephetamol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, (6a*R*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-benzo[c]chromen-1-ol (dronabinol), eptazocine, 8-chloro-6-phenyl-4*H*-[1,2,4]triazolo[4,3-(a)][1,4]benzodiazepine (estazolam), ethoheptazine, ethylmethylthiambutene, ethyl [7-chloro-5-(2-fluorophenyl)-2,3-dihydro-2-oxo-1*H*-1,4-benzodiazepine-3-carboxylate] (ethyl loflazepate), 4,5α-epoxy-3-ethoxy-17-methyl-7-morphinen-6α-ol (ethylmorphine), etonitazene, 4,5α-epoxy-7α-(1-hydroxy-1-methylbutyl)-6-methoxy-17-methyl-6,14-*endo*-etheno-morphinan-3-ol (etorphine), *N*-ethyl-3-phenyl-8,9,10-trinorbornan-2-ylamine (fencamfamine), 7-[2-(α-methylphenethylamino)ethyl]-theophylline) (fenethylline), 3-(α-methylphenethylamino)propionitrile (fenproporex), *N*-(1-phenethyl-4-piperidyl)propionanilide (fentanyl), 7-chloro-5-(2-fluorophenyl)-1-methyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (fludiazepam), 5-(2-fluorophenyl)-1-methyl-7-nitro-1*H*-1,4-benzodiazepin-2(3*H*)-one (flunitrazepam), 7-chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1*H*-1,4-benzodiazepin-2(3*H*)-one (flurazepam), 7-chloro-5-phenyl-1-(2,2,2-trifluoroethyl)-1*H*-1,4-benzodiazepin-2(3*H*)-one (halazepam), 10-bromo-11b-(2-fluorophenyl)-2,3,7,11b-tetrahydro[1,3]oxazolo[3,2-d][1,4]benzodiazepin-6(5*H*)-one (haloxazolam), heroin, 4,5α-epoxy-3-methoxy-17-methyl-6-morphinanone (hydrocodone), 4,5α-epoxy-3-hydroxy-17-methyl-6-morphinanone (hydromorphone), hydroxypethidine, isomethadone, hydroxymethylmorphinan, 11-chloro-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4*H*-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6*H*)-dione (ketazolam), 1-[4-(3-hydroxyphenyl)-1-methyl-4-piperidyl]-1-propanone (ketobemidone), (3*S*,6*S*)-6-dimethylamino-4,4-diphenylheptan-3-yl acetate (levacetylmethadol (LAAM)), (-)-6-dimethylamino-4,4-diphenol-3-heptanone (levomethadone), (-)-17-methyl-3-morphinanol

(levorphanol), levophenacylmorphane, lofentanil, 6-(2-chlorophenyl)-2-(4-methyl-1-piperazinylmethylene)-8-nitro-2*H*-imidazo[1,2-a][1,4]-benzodiazepin-1(4*H*)-one (loprazolam), 7-chloro-5-(2-chlorophenyl)-3-hydroxy-1*H*-1,4-benzodiazepin-2(3*H*)-one (lorazepam), 7-chloro-5-(2-chlorophenyl)-3-hydroxy-1-methyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (lormetazepam), 5-(4-chlorophenyl)-2,5-dihydro-3*H*-imidazo[2,1-*a*]isoindol-5-ol (mazindol), 7-chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (medazepam), *N*-(3-chloropropyl)-α-methylphenethylamine (mefenorex), meperidine, 2-methyl-2-propyltrimethylene dicarbamate (meprobamate), meptazinol, metazocine, methylmorphine, N,α-dimethylphenethylamine (methamphetamine), (±)-6-dimethylamino-4,4-diphenol-3-heptanone (methadone), 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone (methaqualone), methyl [2-phenyl-2-(2-piperidyl)acetate] (methylphenidate), 5-ethyl-1-methyl-5-phenylbarbituric acid (methylphenobarbital), 3,3-diethyl-5-methyl-2,4-piperidinedione (methyprylon), metopon, 8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5*a*][1,4]benzodiazepine (midazolam), 2-(benzhydrylsulfinyl)acetamide (modafinil), 4,5α-epoxy-17-methyl-7-morphinen-3,6α-diol (morphine), myrophine, (±)-*trans*-3-(1,1-dimethylheptyl)-7,8,10,10α-tetrahydro-1-hydroxy-6,6-dimethyl-6*H*-dibenzo-[*b, d*]pyran-9(6α*H*)-one (nabilone), nalbuphene, nalorphine, narceine, nicomorphine, 1-methyl-7-nitro-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (nimetazepam), 7-nitro-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (nitrazepam), 7-chloro-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (nordazepam), norlevorphanol, 6-dimethylamino-4,4-diphenyl-3-hexanone (normethadone), normorphine, norpipanone, the exudation from plants belonging to the species Papaver somniferum (opium), 7-chloro-3-hydroxy-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (oxazepam), (*cis-trans*)-10-chloro-2,3,7,11b-tetrahydro-2-methyl-11b-phenyloxazolo[3,2-*d*][1,4]benzodiazepin-6-(5*H*)-one (oxazolam), 4,5α-epoxy-14-hydroxy-3-methoxy-17-methyl-6-morphinanone (oxycodone), oxymorphone, plants and parts of plants belonging to the species Papaver somniferum (including the subspecies setigerum) (Papaver somniferum), papaveretum, 2-imino-5-phenyl-4-oxazolidinone (pernoline), 1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol (pentazocine), 5-ethyl-5-(1-methylbutyl)-barbituric acid (pentobarbital), ethyl-(1-methyl-4-phenyl-4-piperidinecarboxylate) (pethidine), phenadoxone, phenomorphane, phenazocine, phenoperidine, piminodine, pholcodeine, 3-methyl-2-phenylmorpholine (phenmetrazine), 5-ethyl-5-phenylbarbituric acid (phenobarbital), α,α-dimethylphenethylamine (phentermine), 7-chloro-5-phenyl-1-(2-propynyl)-1*H*-1,4-benzodiazepin-2(3*H*)-one (pinazepam), α-(2-piperidyl)benzhydryl alcohol (pipradrol), 1'-(3-cyano-3,3-diphenylpropyl)[1,4'-bipiperidine]-

4'-carboxamide (piritramide), 7-chloro-1-(cyclopropylmethyl)-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (prazepam), profadol, proheptazine, promedol, properidine, propoxyphene, N-(1-methyl-2-piperidinoethyl)-N-(2-pyridyl)propionamide, methyl {3-[4-methoxycarbonyl-4-(*N*-phenylpropanamido)piperidino]propanoate} (remifentanil), 5-*sec*-butyl-5-ethylbarbituric acid (secbutabarbital), 5-allyl-5-(1-methylbutyl)-barbituric acid (secobarbital), *N*-{4-methoxymethyl-1-[2-(2-thienyl)ethyl]-4-piperidyl}propionanilide (sufentanil), 7-chloro-2-hydroxy-methyl-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (temazepam), 7-chloro-5-(1-cyclohexenyl)-1-methyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (tetrazepam), ethyl (2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate) (tilidine (cis and trans)), tramadol, 8-chloro-6-(2-chlorophenyl)-1-methyl-4*H*-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine (triazolam), 5-(1-methylbutyl)-5-vinylbarbituric acid (vinylbital), (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol, (1R,2R,4S)-2-(dimethylamino)methyl-4-(p-fluorobenzyloxy)-1-(m-methoxyphenyl)cyclohexanol, (1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)phenol, (1S,2S)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol, (2R,3R)-1-dimethylamino-3(3-methoxyphenyl)-2-methyl-pentan-3-ol, (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxyphenyl)-cyclohexane-1,3-diol, preferably as racemate, 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)phenyl 2-(4-isobutoxy-phenyl)-propionate, 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)phenyl 2-(6-methoxy-naphthalen-2-yl)-propionate, 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-(4-isobutyl-phenyl)-propionate, 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-(6-methoxy-naphthalen-2-yl)-propionate, (RR-SS)-2-acetoxy-4-trifluoromethyl-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-4-trifluoromethyl-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-4-chloro-2-hydroxy-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-4-methyl-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-4-methoxy-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-5-nitro-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2',4'-difluoro-3-hydroxy-biphenyl-4-carboxylic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester together with corresponding stereoisomeric compounds, in each case the corresponding derivatives thereof, in particular amides, esters or ethers, and in each case the physiologically acceptable compounds thereof, in particular the salts and solvates thereof, particularly preferably hydrochlorides.

The dosage forms produced according to the invention are particularly suitable for preventing abuse of an opioid active ingredient selected from among the group comprising oxycodone, hydromorphone, morphine, tramadol and the physiologically acceptable derivatives or compounds thereof, preferably the salts and solvates thereof, preferably the hydrochlorides thereof.

The dosage forms produced according to the invention are furthermore in particular suitable for preventing abuse of an opioid active ingredient selected from among the group comprising (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol, (2R,3R)-1-dimethylamino-3-(3-methoxyphenyl)-2-methyl-pentan-3-ol, (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxyphenyl)-cyclohexane-1,3-diol, (1R,2R)-3-(2-dimethylaminonethyl-cyclohexyl)phenol, the physiologically acceptable salts thereof, preferably hydrochlorides, physiologically acceptable enantiomers, stereoisomers, diastereomers and racemates and the physiologically acceptable derivatives thereof, preferably ethers, esters or amides.

These compounds and the process for the production thereof are described in EP-A-693475 and EP-A-780369 respectively. The corresponding descriptions are hereby introduced as a reference and are deemed to be part of the disclosure.

In order to achieve the necessary breaking strength, at least one synthetic or natural polymer (C) which has a breaking strength, measured using the method disclosed in the present application, of at least 500 N is used in the process according to the invention. At least one polymer selected from the group comprising polyalkylene oxides, preferably polymethylene oxide, polyethylene oxide, polypropylene oxide; polyethylene, polypropylene, polyvinyl chloride, polycarbonate, polystyrene, polyacrylate, copolymers thereof, and mixtures of at least two of the stated polymers is preferably used for this purpose. High molecular weight, thermoplastic polyalkylene oxides are preferred. High molecular weight polyethylene oxides with a molecular weight of at least 0.5 million, preferably of at least 1 million to 15 million, determined by rheological measurements, are particularly preferred. These polymers have a viscosity at 25°C of 4500 to 17600 cP, measured on a 5 wt.% aqueous solution using a model RVF Brookfield viscosimeter (spindle no. 2 / rotational speed 2 rpm), of 400 to 4000 cP, measured on a 2 wt.% aqueous solution using the stated viscosimeter (spindle no. 1 or 3 /

rotational speed 10 rpm) or of 1650 to 10000 cP, measured on a 1 wt.% aqueous solution using the stated viscosimeter (spindle no. 2 / rotational speed 2 rpm).

The polymers are preferably used in powder form. They should be soluble in water.

In order to achieve the necessary breaking strength with the processes according to the invention, it is furthermore possible additionally to use at least one natural or synthetic wax (D) with a breaking strength, measured using the method disclosed in the present application, of at least 500 N. Waxes with a softening point of at least 60°C are preferred. Carnauba wax and beeswax are particularly preferred. Carnauba wax is very particularly preferred. Carnauba wax is a natural wax which is obtained from the leaves of the carnauba palm and has a softening point of at least 80°C. When the wax component is additionally used, it is used together with at least one polymer (C) in quantities such that the dosage form produced according to the invention has a breaking strength of at least 500 N.

Component (C) is preferably used in a quantity of 20 to 99.9 wt.%, particularly preferably of at least 30 wt.%, very particularly preferably of at least 40 wt.%, relative to the total weight the dosage form.

Auxiliary substances (B) which may be used are those known auxiliary substances which are conventional for the formulation of solid dosage forms. These are preferably plasticisers, such as triacetin and polyethylene glycol, auxiliary substances which influence active ingredient release, preferably hydrophobic or hydrophilic, preferably hydrophilic polymers, very particularly preferably hydroxypropylmethylcellulose or hydroxypropylcellulose, and/or antioxidants. Polymers, particularly preferably cellulose ethers, cellulose esters and/or acrylic resins are preferably used as hydrophilic matrix materials. Ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxymethylcellulose, poly(meth)acrylic acid and/or the derivatives thereof, such as the salts, amides or esters thereof are very particularly preferably used as matrix materials. Suitable antioxidants are ascorbic acid, butylhydroxyanisole, butylhydroxytoluene, salts of ascorbic acid, monothioglycerol, phosphorous acid, vitamin C, vitamin E and the derivatives thereof, sodium bisulfite, particularly preferably butylhydroxytoluene (BHT) or butylhydroxyanisole (BHA) and α-tocopherol.

The antioxidant is preferably used in quantities of 0.01 to 10 wt.%, preferably of 0.03 to 5 wt.%, relative to the total weight of the dosage form.

To perform the process according to the invention, at least one active ingredient with potential for abuse (A), at least one polymer (C) and optionally a wax (D), optionally at least one of the further optionally present abuse-preventing components (a) to (f) listed below and optionally present auxiliary substances (B) such as antioxidants, plasticisers and/or delayed-release auxiliary substances are processed with the addition of a solvent for the polymer (C) to yield the dosage form.

To this end, components (A), (B), (C) and the optionally present component (D) and optionally at least one of the optionally present further abuse-preventing components (a) to (f) are mixed or, if necessary, separately mixed with addition of component (C) and optionally component (D) and the resultant formulation mixture or the resultant formulation mixtures, after addition of the solvent and optionally after granulation, are shaped to yield the dosage form.

Mixing of components (A), (B), (C) and optionally (D) and of the optionally present further components (a) to (f) with components (C) and the optionally present component (D) optionally proceeds in each case in a mixer known to the person skilled in the art. The mixer may, for example, be a roll mixer, shaking mixer, shear mixer or compulsory mixer.

The solvent for the polymer (C) is added at least in such quantities that the formulation mixture is uniformly moistened.

Solvents which are suitable as the solvent for the polymer (C) are preferably aqueous solvents, such as water, mixtures of water and aliphatic alcohols, preferably alcohols with C_1 to C_6, esters, ethers, hydrocarbons, particularly preferably distilled water, alone or mixed with short-chain alcohols, such as methanol, ethanol, isopropanol, butanol to yield aqueous alcohol solutions.

The solvent is preferably added by stirring. The uniformly moistened composition is then dried. Drying preferably proceeds with exposure to heat at temperatures at which it is possible to rule out any discoloration of the composition. This temperature may be established by simple preliminary testing.

Before or after drying, the composition may be divided into sub-portions which preferably in each case correspond to the mass of a unit of the dosage form. The corresponding dried portions are then shaped to yield the dosage form.

This is preferably achieved by using tablet presses.

The formulation mixture may also be moistened in such a manner that, before addition of the solvent, the formulation mixture is divided, preferably in moulds, into sub-portions, is dispersed in a liquid dispersant with stirring and then the solvent is added. The polymer component (C) is not soluble in the dispersant, which must be miscible with the solvent.

Suitable dispersants are preferably hydrophilic solvents, such as aliphatic alcohols, ketones, esters. Short-chain alcohols are preferably used.

Alternatively, the formulation mixture may also be moistened in such a manner that the solvent may be incorporated into the formulation mixture as a foam. Such a foam of the solvent is preferably produced with the assistance of a high-speed mixer, preferably with the addition of conventional foam stabilisers. Suitable stabilisers are, for example, hydrophilic polymers such as
for example hydroxypropylmethylcellulose.

The foam is also preferably incorporated into the formulation mixture with stirring, a granulated composition so preferably being obtained.

Before or after being divided into sub-portions, which preferably correspond to the mass of a unit of the dosage form, the granulated composition is dried and then shaped into the dosage form.

Drying and shaping may preferably proceed as described above.

The process according to the invention may also be performed in such a manner that solvent is added to the formulation mixture in such a quantity that a shapeable paste is obtained.

Before or after being dried, which may proceed as explained above, such a paste may be divided into sub-portions and the dried portions, after further division in each case into a portion corresponding to the mass of a unit of the dosage form, are shaped or converted to yield the dosage form.

It is here possible to form the sub-portions in the form of strands, which may be produced with the assistance of a screen or a strand former. The dried strands are preferably singulated and shaped to yield the dosage form. This shaping preferably proceeds with the assistance of a tablet press, using shaping rollers or shaping belts equipped with rollers.

It is also possible to convert the paste into a planar structure and to stamp the dosage form out of it once it has dried.

The paste is advantageously processed with an extruder, wherein, depending on the configuration of the extrusion die, strands or planar structures articles are produced, which are singulated by chopping, cutting or stamping. The singulated sub-portions may be shaped or formed as described above to yield the dosage form. Corresponding apparatuses are known to the person skilled in the art.

The process according to the invention may here be performed continuously or discontinuously.

It is also possible to add solvent to the formulation mixture in such a quantity that at least the polymer component (C) is dissolved. Such a solution or dispersion/suspension is preferably converted into a planar structure, an extruder with a flat die preferably being used or the solution being cast onto a planar support.

As stated above, after drying, the dosage forms may be obtained from the planar structures by stamping or calendering. It is also possible, as stated above, to convert the solution into strands and to singulate these, preferably after they have been dried, and shape them to yield the dosage form.

Alternatively, the solution may also be divided into portions such that, after drying, they each correspond to the mass of a unit of the dosage form, with moulds which already correspond to the shape of the unit of the dosage form preferably being used for this purpose.

If the solution is divided into any desired portions, the portions may, after drying, optionally be combined again and be shaped to form the dosage form, being for example packaged in a capsule or press-moulded to form a tablet.

The formulation mixtures combined with solvent are preferably processed at temperatures of 20°C to 40°C, wherein, apart from during drying to remove the solvent and the optionally present dispersant, no higher temperatures are used. After shaping to yield the dosage form, further drying corresponding to the above-described drying may optionally be performed.

As already explained, the dosage form produced according to the invention may assume multiparticulate form, preferably the form of microtablets, microcapsules, micropellets, granules, spheroids, beads or pellets, optionally packaged in capsules or press-moulded into tablets, preferably for oral administration. The multiparticulate forms preferably have a size or size distribution in the range from 0.1 to 3 mm, particularly preferably in the range from 0.5 to 2 mm. Depending on the desired dosage form, conventional auxiliary substances (B) are optionally also used for the formulation of the dosage form.

The dosage forms obtained by the process according to the invention are distinguished in that, by virtue of their hardness of at least 500 N, they cannot be pulverised with the assistance of conventional comminution means available to an abuser, such as a pestle and mortar. This virtually rules out oral, parenteral, in particular intravenous, or nasal abuse. However, in order to prevent any possible abuse of the dosage forms produced according to the invention, in a preferred embodiment, the dosage forms according to the invention may contain further abuse-complicating or -preventing agents as auxiliary substances (B).

The abuse-proofed dosage form produced according to the invention, which comprises, apart from one or more active ingredients with potential for abuse (A), at least one hardening polymer (C) and optionally at least one wax (D), may accordingly also comprise at least one of the following components (a)-(e) as auxiliary substances (B):

(a) at least one substance which irritates the nasal passages and/or pharynx,

(b) at least one viscosity-increasing agent, which, with the assistance of a necessary minimum quantity of an aqueous liquid, preferably as an aqueous extract obtained from the dosage form, forms a gel which preferably remains visually distinguishable when introduced into a further quantity of an aqueous liquid,

(c) at least one antagonist for each of the active ingredients with potential for abuse,

(d) at least one emetic,

(e) at least one dye as an aversive agent,

(f) at least one bitter substance.

Components (a) to (f) are additionally each individually suitable for abuse-proofing the dosage form obtained according to the invention. Accordingly, component (a) is preferably suitable for proofing the dosage form against nasal, oral and/or parenteral, preferably intravenous, abuse, component (b) is preferably suitable for proofing against parenteral, particularly preferably intravenous and/or nasal abuse, component (c) is preferably suitable for proofing against nasal and/or parenteral, particularly preferably intravenous, abuse, component (d) is preferably suitable for proofing against parenteral, particularly preferably intravenous, and/or oral and/or nasal abuse, component (e) is suitable as a visual deterrent against oral or parenteral abuse and component (f) is suitable for proofing against oral or nasal abuse. Combined use according to the invention of at least one of the above-stated components makes it possible still more effectively to prevent abuse of dosage forms obtained by the process according to the invention.

For example, the dosage form obtained according to the invention may also comprise two or more of components (a)-(f) in a combination, preferably (a), (b) and optionally (c) and/or (f) and/or (e) or (a), (b) and optionally (d) and/or (f) and/or (e).

In another embodiment, the dosage form obtained according to the invention may comprise all of components (a)-(f).

If the dosage form obtained according to the invention comprises an abuse-preventing component (a), substances which irritate the nasal passages and/or pharynx which may be considered according to the invention are any substances which, when administered accordingly via the nasal passages and/or pharynx, bring about a physical reaction which is either so unpleasant for the abuser that he/she does not wish to or cannot continue administration, for example burning, or physiologically counteracts taking of the corresponding active ingredient, for example due to increased nasal secretion or sneezing. These substances which conventionally irritate the nasal passages and/or pharynx may also bring about a very unpleasant sensation or even unbearable pain when administered parenterally, in particular intravenously, such that the abuser does not wish to or cannot continue taking the substance.

Particularly suitable substances which irritate the nasal passages and/or pharynx are those which cause burning, itching, an urge to sneeze, increased formation of secretions or a combination of at least two of these stimuli. Appropriate substances and the quantities thereof which are conventionally to be used are known per se to the person skilled in the art or may be identified by simple preliminary testing.

The substance which irritates the nasal passages and/or pharynx of component (a) is preferably based on one or more constituents or one or more plant parts of at least one hot substance drug.

Corresponding hot substance drugs are known per se to the person skilled in the art and are described, for example, in "Pharmazeutische Biologie - Drogen und ihre Inhaltsstoffe" by Prof. Dr. Hildebert Wagner, 2nd., revised edition, Gustav Fischer Verlag, Stuttgart-New York,

1982, pages 82 et seq.. The corresponding description is hereby introduced as a reference and is deemed to be part of the disclosure.

A dosage unit is taken to mean a separate or separable administration unit, such as for example a tablet or a capsule.

One or more constituents of at least one hot substance drug selected from the group consisting of Allii sativi bulbus (garlic), Asari rhizoma cum herba (Asarum root and leaves), Calami rhizoma (calamus root), Capsici fructus (capsicum), Capsici fructus acer (cayenne pepper), Curcumae longae rhizoma (turmeric root), Curcumae xanthorrhizae rhizoma (Javanese turmeric root), Galangae rhizoma (galangal root), Myristicae semen (nutmeg), Piperis nigri fructus (pepper), Sinapis albae semen (white mustard seed), Sinapis nigri semen (black mustard seed), Zedoariae rhizoma (zedoary root) and Zingiberis rhizoma (ginger root), particularly preferably from the group consisting of Capsici fructus (capsicum), Capsici fructus acer (cayenne pepper) and Piperis nigri fructus (pepper) may preferably be added as component (a) to the dosage form according to the invention.

The constituents of the hot substance drugs preferably comprise o-methoxy(methyl)phenol compounds, acid amide compounds, mustard oils or sulfide compounds or compounds derived therefrom.

Particularly preferably, at least one constituent of the hot substance drugs is selected from the group consisting of myristicin, elemicin, isoeugenol, α-asarone, safrole, gingerols, xanthorrhizol, capsaicinoids, preferably capsaicin, capsaicin derivatives, such as N-vanillyl-9E-octadecenamide, dihydrocapsaicin, nordihydrocapsaicin, homocapsaicin, norcapsaicin and nomorcapsaicin, piperine, preferably trans-piperine, glucosinolates, preferably based on non-volatile mustard oils, particularly preferably based on p-hydroxybenzyl mustard oil, methylmercapto mustard oil or methylsulfonyl mustard oil, and compounds derived from these constituents.

The dosage form obtained according to the invention may preferably contain the plant parts of the corresponding hot substance drugs in a quantity of 0.01 to 30 wt.%, particularly preferably of 0.1 to 0.5 wt.%, in each case relative to the total weight of the dosage unit.

If one or more constituents of corresponding hot substance drugs are used, the quantity thereof in a dosage unit obtained according to the invention preferably amounts to 0.001 to 0.005 wt.%, relative to the total weight of the dosage unit.

Another option for preventing abuse of the dosage form obtained according to the invention consists in adding at least one viscosity-increasing agent as a further abuse-preventing component (b) to the dosage form, which, with the assistance of a necessary minimum quantity of an aqueous liquid, preferably as an aqueous extract obtained from the dosage form, forms a gel which is virtually impossible to administer safely and preferably remains visually distinguishable when introduced into a further quantity of an aqueous liquid.

For the purposes of the present invention, visually distinguishable means that the active ingredient-containing gel formed with the assistance of a necessary minimum quantity of aqueous liquid, when introduced, preferably with the assistance of a hypodermic needle, into a further quantity of aqueous liquid at 37°C, remains substantially insoluble and cohesive and cannot straightforwardly be dispersed in such a manner that it can safely be administered parenterally, in particular intravenously. The material preferably remains visually distinguishable for at least one minute, preferably for at least 10 minutes.

The increased viscosity of the extract makes it more difficult or even impossible for it to be passed through a needle or injected. If the gel remains visually distinguishable, this means that the gel obtained on introduction into a further quantity of aqueous liquid, for example by injection into blood, initially remains in the form of a largely cohesive thread, which, while it may indeed be broken up mechanically into smaller fragments, cannot be dispersed or even dissolved in such a manner that it can safely be administered parenterally, in particular intravenously. In combination with at least one optionally present component (a) to (e), this additionally leads to unpleasant burning, vomiting, bad flavour and/or visual deterrence.

Intravenous administration of such a gel would most probably result in obstruction of blood vessels, associated with serious damage to the health of the abuser.

In order to verify whether a viscosity-increasing agent is suitable as component (b) for use in the dosage form obtained according to the invention, the active ingredient is mixed with the viscosity-increasing agent and suspended in 10 ml of water at a temperature of 25°C. If this results in the formation of a gel which fulfils the above-stated conditions, the corresponding viscosity-increasing agent is suitable for additionally preventing or averting abuse of the dosage forms obtained according to the invention.

If component (b) is added to the dosage form obtained according to the invention, one or more viscosity-increasing agents are used which are selected from the group comprising microcrystalline cellulose with 11 wt.% carboxymethylcellulose sodium (Avicel® RC 591), carboxymethylcellulose sodium (Blanose®, CMC-Na C300P®, Frimulsion BLC-5®, Tylose C300 P®), polyacrylic acid (Carbopol® 980 NF, Carbopol® 981), locust bean flour (Cesagum® LA-200, Cesagum® LID/150, Cesagum® LN-1), pectins, preferably from pectin fruit and apples (Cesapectin® HM Medium Rapid Set), waxy maize starch (C*Gel 04201®), sodium alginate (Frimulsion ALG (E401)®), guar flour (Frimulsion BM®, Polygum 26/1-75®), iota carrageenan (Frimulsion D021®), karaya gum, gellan gum (Kelcogel F®, Kelcogel LT100®), galactomannan (Meyprogat 150®), tara stone flour (Polygum 43/1®), propylene glycol alginate (Protanal-Ester SD-LB®), sodium hyaluronate, tragacanth, tara gum (Vidogum SP 200®), fermented polysaccharide welan gum (K1A96), xanthan gum (Xantural 180®). Xanthans are particularly preferred. The names stated in brackets are the trade names by which the materials are known commercially. In general, a quantity of 0.1 to 20 wt.%, particularly preferably of 0.1 to 15 wt.%, relative to the total weight of the dosage form, of the stated viscosity-increasing agent(s) is sufficient to fulfil the above-stated conditions.

The component (b) viscosity-increasing agents, where provided, are preferably present in the dosage form obtained according to the invention in quantities of ≥ 5 mg per dosage unit, i.e. per administration unit.

In a particularly preferred embodiment of the present invention, the viscosity-increasing agents used as component (b) are those which, on extraction from the dosage form with the necessary minimum quantity of aqueous liquid, form a gel which encloses air bubbles. The resultant gels are distinguished by a turbid appearance, which provides the potential abuser

with an additional optical warning and discourages him/her from administering the gel parenterally.

Component (C) may also optionally serve as an additional viscosity-increasing agent, which forms a gel with the assistance of a necessary minimum quantity of aqueous liquid.

It is also possible to formulate the viscosity-increasing agents and the other constituents in the dosage form obtained according to the invention in a mutually spatially separated arrangement.

In order to discourage and prevent abuse, the dosage form obtained according to the invention may furthermore comprise component (c), namely one or more antagonists for the active ingredient or active ingredients with potential for abuse, wherein the antagonists are preferably spatially separated from the remaining constituents of the dosage form obtained according to the invention and, when correctly used, do not exert any effect.

Suitable antagonists for preventing abuse of the active ingredients are known per se to the person skilled in the art and may be present in the dosage form according to the invention as such or in the form of corresponding derivatives, in particular esters or ethers, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the salts or solvates thereof.

If the active ingredient present in the dosage form is an opioid, the antagonist used is preferably an antagonist selected from the group comprising naloxone, naltrexone, nalmefene, nalid, nalmexone, nalorphine or naluphine, in each case optionally in the form of a corresponding physiologically acceptable compound, in particular in the form of a base, a salt or solvate. The corresponding antagonists, where component (c) is provided, are preferably used in a quantity of $\geq$ 1 mg, particularly preferably in a quantity of 3 to 100 mg, very particularly preferably in a quantity of 5 to 50 mg per dosage form, i.e. per administration unit.

If the dosage form obtained according to the invention comprises a stimulant as active ingredient, the antagonist is preferably a neuroleptic, preferably at least one compound selected from the group consisting of haloperidol, promethazine, fluphenazine, perphenazine,

levomepromazine, thioridazine, perazine, chlorpromazine, chlorprothixine, zuclopentixol, flupentixol, prothipendyl, zotepine, benperidol, pipamperone, melperone and bromperidol.

The dosage form obtained according to the invention preferably comprises these antagonists in a conventional therapeutic dose known to the person skilled in the art, particularly preferably in a quantity of twice to three times the conventional dose per administration unit.

If the combination to further discourage and prevent abuse of the dosage form produced according to the invention also comprises component (d), it may comprise at least one emetic, which is preferably present in a spatially separated arrangement from the other components of the dosage form produced according to the invention and, when correctly used, is intended not to exert its effect in the body.

Suitable emetics for additionally preventing abuse of an active ingredient are known per se to the person skilled in the art and may be present in the dosage form obtained according to the invention as such or in the form of corresponding derivatives, in particular esters or ethers, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the salts or solvates thereof.

An emetic based on one or more constituents of ipecacuanha (ipecac) root, preferably based on the constituent emetine may preferably be considered in the dosage form obtained according to the invention, as are, for example, described in "Pharmazeutische Biologie - Drogen und ihre Inhaltsstoffe" by Prof. Dr. Hildebert Wagner, 2nd, revised edition, Gustav Fischer Verlag, Stuttgart, New York, 1982. The corresponding literature description is hereby introduced as a reference and is deemed to be part of the disclosure.

The dosage form obtained according to the invention may preferably comprise the emetic emetine as component (d), preferably in a quantity of $\geq$ 3 mg, particularly preferably of $\geq$ 10 mg and very particularly preferably in a quantity of $\geq$ 20 mg per dosage form, i.e. administration unit.

Apomorphine may likewise preferably be used as an emetic for additional abuse-proofing, preferably in a quantity of preferably ≥ 3 mg , particularly preferably of ≥ 5 mg and very particularly preferably of ≥ 7 mg per administration unit.

If the dosage form obtained according to the invention contains component (e) as an additional abuse-preventing auxiliary substance, the use of such a dye brings about an intense coloration of a corresponding aqueous solution, in particular when the attempt is made to extract the active ingredient for parenteral, preferably intravenous administration, which coloration may act as a deterrent to the potential abuser. Oral abuse, which conventionally begins by means of aqueous extraction of the active ingredient, may also be prevented by this coloration. Suitable dyes and the quantities required for the necessary deterrence may be found in WO 03/015531, wherein the corresponding disclosure should be deemed to be part of the present disclosure and is hereby introduced as a reference.

If the dosage form obtained according to the invention contains component (f) as an additional abuse-preventing auxiliary substance, this addition of at least one bitter substance and the consequent impairment of the flavour of the dosage form additionally prevents oral and/or nasal abuse.

Suitable bitter substances and the quantities effective for use may be found in US-2003/0064099 A1, the corresponding disclosure of which should be deemed to be the disclosure of the present application and is hereby introduced as a reference. Suitable bitter substances are preferably aromatic oils, preferably peppermint oil, eucalyptus oil, bitter almond oil, menthol, fruit aroma substances, preferably aroma substances from lemons, oranges, limes, grapefruit or mixtures thereof, and/or denatonium benzoate (Bitrex®). Denatonium benzoate is particularly preferred.

The solid dosage form obtained according to the invention is suitable not only for oral, but also for vaginal or rectal administration, but is preferably for oral intake. The dosage form is preferably not in film form. The dosage form according to the invention may assume multiparticulate form, preferably cylindrical form, the form of microtablets, microcapsules, micropellets, granules, spheroids, beads or pellets, optionally packaged in capsules or press-moulded into tablets, preferably for oral administration. The multiparticulate forms preferably

have a size or size distribution in the range from 0.1 to 3 mm, particularly preferably in the range from 0.5 to 2 mm. Depending on the desired dosage form, conventional auxiliary substances (B) are optionally also used for the formulation of the dosage form.

In a further preferred embodiment, the dosage form obtained according to the invention assumes the form of a tablet, a capsule or is in the form of an oral osmotic therapeutic system (OROS), preferably if at least one further abuse-preventing component (a)-(f) is also present.

If components (c) and/or (d) and/or (f) are present in the dosage form obtained according to the invention, care must be taken to ensure that they are formulated in such a manner or are present in such a low dose that, when correctly administered, the dosage form is able to bring about virtually no effect which impairs the patient or the efficacy of the active ingredient.

If the dosage form obtained according to the invention contains component (d) and/or (f), the dosage must be selected such that, when correctly orally administered, no negative effect is caused. If, however, the intended dosage is exceeded in the event of abuse, nausea or an inclination to vomit or a bad flavour are produced The particular quantity of component (d) and/or (f) which can still be tolerated by the patient in the event of correct oral administration may be determined by the person skilled in the art by simple preliminary testing.

If, however, irrespective of the fact that the further dosage form produced according to the invention is virtually impossible to pulverise, components (c) and/or (d) and/or (f) are used to protect the dosage form, these components should preferably be used at a dosage which is sufficiently high that, when abusively administered, they bring about an intense negative effect on the abuser. This is preferably achieved by spatial separation of at least the active ingredient or active ingredients from components (c) and/or (d) and/or (f), wherein the active ingredient or active ingredients is/are present in at least one subunit (X) and components (c) and/or (d) and/or (f) is/are present in at least one subunit (Y), and wherein, when the dosage form is correctly administered, components (c), (d) and (f) do not exert their effect on taking and/or in the body and the remaining components of the formulation, in particular component (C) and optionally (D), are identical.

If the dosage form obtained according to the invention comprises at least 2 of components (c) and (d) or (f), these may each be present in the same or different subunits (Y). Preferably, when present, all the components (c) and (d) and (f) are present in one and the same subunit (Y).

For the purposes of the present invention, subunits are solid formulations, which in each case, apart from conventional auxiliary substances known to the person skilled in the art, contain the active ingredient(s), at least one polymer (C) and the optionally present component (D) and optionally at least one of the optionally present components (a) and/or (b) and/or (e) or in each case at least one polymer (C) and optionally (D) and the antagonist(s) and/or emetic(s) and/or component (e) and/or component (f) and optionally at least one of the optionally present components (a) and/or (b). Care must here be taken to ensure that each of the stated subunits is formulated in accordance with the above-stated process according to the invention.

One substantial advantage of the separated formulation of active ingredients from components (c) or (d) or (f) in subunits (X) and (Y) of the dosage form produced according to the invention is that, when correctly administered, components (c) and/or (d) and/or (f) are hardly released on taking and/or in the body or are released in such small quantities that they exert no effect which impairs the patient or therapeutic success or, on passing through the patient's body, they are only liberated in locations where they cannot be sufficiently absorbed to be effective. When the dosage form is correctly administered, preferably hardly any of components (c) and/or (d) and/or (f) is released into the patient's body or they go unnoticed by the patient.

The person skilled in the art will understand that the above-stated conditions may vary as a function of the particular components (c), (d) and/or (f) used and of the formulation of the subunits or the dosage form. The optimum formulation for the particular dosage form may be determined by simple preliminary testing. What is vital is that each subunit contains the polymer (C) and optionally component (D) and has been formulated in the stated manner and produced according to the invention.

Should, contrary to expectations, the abuser succeed in comminuting such a dosage form produced according to the invention, which comprises components (c) and/or (e) and/or (d)

and/or (f) in subunits (Y), for the purpose of abusing the active ingredient and obtain a powder which is extracted with a suitable extracting agent, not only the active ingredient but also the particular component (c) and/or (e) and/or (f) and/or (d) will be obtained in a form in which it cannot readily be separated from the active ingredient, such that when the dosage form which has been tampered with is administered, in particular by oral and/or parenteral administration, it will exert its effect on taking and/or in the body combined with an additional negative effect on the abuser corresponding to component (c) and/or (d) and/or (f) or, when the attempt is made to extract the active ingredient, the coloration will act as a deterrent and so prevent abuse of the dosage form.

A dosage form in which the active ingredient or active ingredients is/are spatially separated from components (c), (d) and/or (e), preferably by formulation in different subunits, may be formulated according to the invention in many different ways, wherein the corresponding subunits in the dosage form may each be present in any desired spatial arrangement relative to one another, provided that the above-stated conditions for the release of components (c) and/or (d) are fulfilled.

The person skilled in the art will understand that component(s) (a) and/or (b) which are optionally also present may preferably be formulated in the dosage form produced according to the invention both in the particular subunits (X) and (Y) and in the form of independent subunits corresponding to subunits (X) and (Y), provided that neither the abuse-proofing nor the active ingredient release in the event of correct administration is impaired by the nature of the formulation and the polymer (C) and optionally (D) is preferably included in the formulation and formulation is carried out in accordance with the above-stated process in order to achieve the necessary hardness.

In a preferred embodiment of the dosage form produced according to the invention, subunits (X) and (Y) are present in multiparticulate form, wherein microtablets, microcapsules, micropellets, granules, spheroids, beads or pellets are preferred and the same form, i.e. shape, is selected for both subunit (X) and subunit (Y), such that it is not possible to separate subunits (X) from (Y), for example by mechanical selection. The multiparticulate forms are preferably of a size in the range from 0.1 to 3 mm, preferably of 0.5 to 2 mm.

The subunits (X) and (Y) in multiparticulate form may also preferably be packaged in a capsule or be press-moulded into a tablet, wherein the final formulation in each case proceeds in such a manner that the subunits (X) and (Y) are also retained in the resultant dosage form.

The multiparticulate subunits (X) and (Y) of identical shape should also not be visually distinguishable from one another so that the abuser cannot separate them from one another by simple sorting. This may, for example, be achieved by the application of identical coatings which, apart from this disguising function, may also incorporate further functions, such as, for example, delayed release of one or more active ingredients or provision of a finish resistant to gastric juices on the particular subunits.

The multiparticulate subunits may also be formulated as an oral dosage form as a slurry or suspension in pharmaceutically safe suspending media.

In a further preferred embodiment of the present invention, subunits (X) and (Y) are in each case arranged in layers relative to one another.

The layered subunits (X) and (Y) are preferably arranged for this purpose vertically or horizontally relative to one another in the dosage form produced according to the invention, wherein in each case one or more layered subunits (X) and one or more layered subunits (Y) may be present in the dosage form, such that, apart from the preferred layer sequences (X)-(Y) or (X)-(Y)-(X), any desired other layer sequences may be considered, optionally in combination with layers containing components (a) and/or (b).

Another preferred dosage form produced according to the invention is one in which subunit (Y) forms a core which is completely enclosed by subunit (X), wherein a separation layer (Z) may be present between said layers. Such a structure is preferably also suitable for the above-stated multiparticulate forms, wherein both subunits (X) and (Y) and an optionally present separation layer (Z), which must satisfy the hardness requirement according to the invention, are formulated in one and the same multiparticulate form.
In a further preferred embodiment of the dosage form produced according to the invention, the subunit (X) forms a core, which is enclosed by subunit (Y), wherein the latter comprises at least one channel which leads from the core to the surface of the dosage form.

The dosage form produced according to the invention may comprise, between one layer of the subunit (X) and one layer of the subunit (Y), in each case one or more, preferably one, optionally swellable separation layer (Z) which serves to separate subunit (X) spatially from (Y).

If the dosage form produced according to the invention comprises the layered subunits (X) and (Y) and an optionally present separation layer (Z) in an at least partially vertical or horizontal arrangement, the dosage form preferably takes the form of a tablet or a laminate.

In one particularly preferred embodiment, the entirety of the free surface of subunit (Y) and optionally at least part of the free surface of subunit(s) (X) and optionally at least part of the free surface of the optionally present separation layer(s) (Z) may be coated with at least one barrier layer (Z') which prevents release of component (c) and/or (e) and/or (d) and/or (f). The barrier layer (Z') must also fulfil the hardness conditions according to the invention.

Another particularly preferred embodiment of the dosage form produced according to the invention comprises a vertical or horizontal arrangement of the layers of subunits (X) and (Y) and at least one push layer (p) arranged there between, and optionally a separation layer (Z), in which dosage form the entirety of the free surface of the layer structure consisting of subunits (X) and (Y), the push layer and the optionally present separation layer (Z) is provided with a semipermeable coating (E), which is permeable to a release medium, i.e. conventionally a physiological liquid, but substantially impermeable to the active ingredient and to component (c) and/or (d) and/or (f), and wherein this coating (E) comprises at least one opening for release of the active ingredient in the area of subunit (X).

A corresponding dosage form is known to the person skilled in the art, for example under the name oral osmotic therapeutic system (OROS), as are suitable materials and methods for the production thereof, inter alia from US 4,612,008, US 4,765,989 and US 4,783,337. The corresponding descriptions are hereby introduced as a reference and are deemed to be part of the disclosure.

In a further preferred embodiment, the subunit (X) of the dosage form produced according to the invention is in the form of a tablet, the edge face and optionally one of the two main faces of which is covered with a barrier layer (Z') containing component (c) and/or (d) and/or (f).

The person skilled in the art will understand that the auxiliary substances of the subunit(s) (X) or (Y) and of the optionally present separation layer(s) (Z) and/or of the barrier layer(s) (Z') used in the formulation according to the invention of the dosage form will vary as a function of the arrangement thereof in the dosage form, the mode of administration and as a function of the particular active ingredient of the optionally present components (a) and/or (b) and/or (e) and of component (c) and/or (d) and/or (f). The materials which have the requisite properties are in each case known per se to the person skilled in the art.

If release of component (c) and/or (d) and/or (f) from subunit (Y) of the dosage form produced according to the invention is prevented with the assistance of a cover, preferably a barrier layer, the subunit may consist of conventional materials known to the person skilled in the art, providing that it contains at least one polymer (C) and optionally (D) to fulfil the hardness condition and has been produced according to the invention.

If a corresponding barrier layer (Z') is not provided to prevent release of component (c) and/or (d) and/or (f), the materials of the subunits should be selected such that release of the particular component (c) and/or (d) from subunit (Y) is virtually ruled out.
The materials which are stated below to be suitable for production of the barrier layer may preferably be used for this purpose.

Preferred materials are those which are selected from the group comprising alkylcelluloses, hydroxyalkylcelluloses, glucans, scleroglucans, mannans, xanthans, copolymers of poly[bis(p-carboxyphenoxy)propane and sebacic acid, preferably in a molar ratio of 20:80 (commercially available under the name Polifeprosan 20®), carboxymethylcelluloses, cellulose ethers, cellulose esters, nitrocelluloses, polymers based on (meth)acrylic acid and the esters thereof, polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, halogenated polyvinyls, polyglycolides, polysiloxanes and polyurethanes and the copolymers thereof.

Particularly suitable materials may be selected from the group comprising methylcellulose, ethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxybutylmethylcellulose, cellulose acetate, cellulose propionate (of low, medium or high molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxymethylcellulose, cellulose triacetate, sodium cellulose sulfate, polymethyl methacrylate, polyethyl methacrylate, polybutyl methacrylate, polyisobutyl methacrylate, polyhexyl methacrylate, polyisodecyl methacrylate, polylauryl methacrylate, polyphenyl methacrylate, polymethyl acrylate, polyisopropyl acrylate, polyisobutyl acrylate, polyoctadecyl acrylate, polyethylene, low density polyethylene, high density polyethylene, polypropylene, polyethylene glycol, polyethylene oxide, polyethylene terephthalate, polyvinyl alcohol, polyvinyl isobutyl ether, polyvinyl acetate and polyvinyl chloride.

Particularly suitable copolymers may be selected from the group comprising copolymers of butyl methacrylate and isobutyl methacrylate, copolymers of methyl vinyl ether and maleic acid of high molecular weight, copolymers of methyl vinyl ether and maleic acid monoethyl ester, copolymers of methyl vinyl ether and maleic anhydride and copolymers of vinyl alcohol and vinyl acetate.

Further materials which are particularly suitable for formulating the barrier layer are starch-filled polycaprolactone (WO98/20073), aliphatic polyesteramides (DE 19 753 534 A1, DE 19 800 698 A1, EP 0 820 698 A1), aliphatic and aromatic polyester urethanes (DE 19822979), polyhydroxyalkanoates, in particular polyhydroxybutyrates, polyhydroxyvalerates, casein (DE 4 309 528), polylactides and copolylactides (EP 0 980 894 A1). The corresponding descriptions are hereby introduced as a reference and are deemed to be part of the disclosure.

The above-stated materials may optionally be blended with further conventional auxiliary substances known to the person skilled in the art, preferably selected from the group comprising glyceryl monostearate, semi-synthetic triglyceride derivatives, semi-synthetic glycerides, hydrogenated castor oil, glyceryl palmitostearate, glyceryl behenate, polyvinylpyrrolidone, gelatine, magnesium stearate, stearic acid, sodium stearate, talcum, sodium benzoate, boric acid and colloidal silica, fatty acids, substituted triglycerides, glycerides, polyoxyalkylene glycols and the derivatives thereof.

If the dosage form produced according to the invention comprises a separation layer (Z'), said layer, like the uncovered subunit (Y), may preferably consist of the above-stated materials described for the barrier layer. The person skilled in the art will understand that release of the active ingredient or of component (c) and/or (d) from the particular subunit may be controlled by the thickness of the separation layer.

The dosage form produced according to the invention exhibits controlled release of the active ingredient. It is preferably suitable for twice daily administration to patients.

The dosage form produced according to the invention may comprise one or more active ingredients with potential for abuse at least partially in a further delayed-release form, wherein delayed release may be achieved with the assistance of conventional materials and methods known to the person skilled in the art, for example by embedding the active ingredient in a delayed-release matrix or by the application of one or more delayed-release coatings. Active ingredient release must, however, be controlled such that the above-stated conditions are fulfilled in each case, for example that, in the event of correct administration of the dosage form, the active ingredient or active ingredients are virtually completely released before the optionally present component (c) and/or (d) can exert an impairing effect. Addition of materials effecting controlled release must moreover not impair the necessary hardness.

Controlled release from the dosage form obtained according to the invention is preferably achieved by embedding the active ingredient in a matrix. The auxiliary substances acting as matrix materials control active ingredient release. Matrix materials may, for example, be hydrophilic, gel-forming materials, from which active ingredient release proceeds mainly by diffusion, or hydrophobic materials, from which active ingredient release proceeds mainly by diffusion from the pores in the matrix.

Physiologically acceptable, hydrophobic materials which are known to the person skilled in the art may be used as matrix materials. Polymers, particularly preferably cellulose ethers, cellulose esters and/or acrylic resins are preferably used as hydrophilic matrix materials. Ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxymethylcellulose, poly(meth)acrylic acid and/or the derivatives thereof, such as the salts, amides or esters thereof are very particularly preferably used as matrix materials.

Matrix materials prepared from hydrophobic materials, such as hydrophobic polymers, waxes, fats, long-chain fatty acids, fatty alcohols or corresponding esters or ethers or mixtures thereof are also preferred. Mono- or diglycerides of C12-C30 fatty acids and/or C12-C30 fatty alcohols and/or waxes or mixtures thereof are particularly preferably used as hydrophobic materials.

It is also possible to use mixtures of the above-stated hydrophilic and hydrophobic materials as matrix materials.

Component (C) and the optionally present component (D), which serve to achieve the breaking strength of at least 500 N which is necessary according to the invention, may furthermore themselves serve as additional matrix materials.

If the dosage form produced according to the invention is intended for oral administration, it may also preferably comprise a coating which is resistant to gastric juices and dissolves as a function of the pH value of the release environment.
By means of this coating, it is possible to ensure that the dosage form produced according to the invention passes through the stomach undissolved and the active ingredient is only released in the intestines. The coating which is resistant to gastric juices preferably dissolves at a pH value of between 5 and 7.5.

Corresponding materials and methods for the delayed release of active ingredients and for the application of coatings which are resistant to gastric juices are known to the person skilled in the art, for example from "Coated Pharmaceutical Dosage Forms - Fundamentals, Manufacturing Techniques, Biopharmaceutical Aspects, Test Methods and Raw Materials" by Kurt H. Bauer, K. Lehmann, Hermann P. Osterwald, Rothgang, Gerhart, 1st edition, 1998, Medpharm Scientific Publishers. The corresponding literature description is hereby introduced as a reference and is deemed to be part of the disclosure.

Method for determining breaking strength

In order to verify whether a material may be used as component (C) or (D), the material is dissolved in a tablet mould with the assistance of a solvent for component (C) or (D) and, once the solvent has been removed at temperatures below the softening point of the material, is pressed to form a tablet with a diameter of 10 mm and a height of 5 mm using a force of 150 N.

Using tablets produced in this manner, breaking strength is determined with the apparatus described below in accordance with the method for determining the breaking strength of tablets published in the European Pharmacopoeia 1997, page 143, 144, method no. 2.9.8. The apparatus used for the measurement is a "Zwick Z 2.5" materials tester, Fmax = 2.5 kN with a maximum draw of 1150 mm, which should be set up with 1 column and 1 spindle, a clearance behind of 100 mm and a test speed adjustable between 0.1 and 800 mm/min together with testControl software. Measurement is performed using a pressure piston with screw-in inserts and a cylinder (diam. 10 mm), a force transducer, Fmax. 1 kN, diameter = 8 mm, class 0.5 from 10 N, class 1 from 2 N to ISO 7500-1, with manufacturer's test certificate M to DIN 55350-18 (Zwick gross force Fmax = 1.45 kN) (all apparatus from Zwick GmbH & Co. KG, Ulm, Germany) with order no. BTC-FR 2.5 TH. D09 for the tester, order no. BTC-LC 0050N. P01 for the force transducer, order no. BO 70000 S06 for the centring device.

Figure 1 shows the measurement of the breaking strength of a tablet, in particular the tablet (4) adjustment device (6) used for this purpose before and during the measurement. To this end, the tablet (4) is held between the upper pressure plate (1) and the lower pressure plate (3) of the force application apparatus (not shown) with the assistance of two 2-part clamping devices, which are in each case firmly fastened (not shown) with the upper and lower pressure plate once the spacing (5) necessary for accommodating and centring the tablet to be measured has been established. The spacing (5) may be established by moving the 2-part clamping devices horizontally outwards or inwards in each case on the pressure plate on which they are mounted.

The tablets deemed to be resistant to breaking under a specific load include not only those which have not broken but also those which may have suffered plastic deformation under the action of the force.

The breaking strength of the dosage forms obtained according to the invention is determined by the stated measurement method for determining breaking strength, with dosage forms other than tablets also being tested.

The invention is explained below with reference to Examples. These explanations are given merely by way of example and do not restrict the general concept of the invention.

Examples

Example 1

	Per tablet	Complete batch
Tramadol HCl	100.0 mg	1495.0 g
Polyethylene oxide, MW 7 000 000 (Polyox WSR 303 from Dow)	167.8 mg	2508.6 g
Hydroxypropylmethylcellulose (Hypromellose 100 000 mPa)	33.5 mg	500.8 g
Butylhydroxytoluene (BHT)	0.2 mg	3.0 g
Total mass	300.5 mg	4507.4 g

The stated quantity of BHT was dissolved in ethanol (96%), such that a 7.7% (mass/mass) ethanolic solution was obtained. This was mixed initially with 150 g of polyethylene oxide in a high speed mixer for 30 minutes and then the remaining quantity of polyethylene oxide was added and stirring continued for a further 30 minutes. The composition was dried for 12 h at 40°C.

All the further components were added and mixed for 15 min in a free-fall mixer. The powder mixture was divided between moulds, each having a diameter of 13 mm and a depth of 6 mm. Using a syringe with cannula, the mixture was suspended in each case in 0.5 ml of 96% ethanol and then in each case combined with 0.5 ml of distilled water After 24 hours' swelling time, the swollen composition was dried for 24 h at 40°C.

The divided up, dried portions were each press-moulded into tablets using a model EK 0 eccentric press. The tabletting tool had a diameter of 10 mm and a radius of curvature of 8 mm.

The breaking strength of the tablets was determined using the above-described method. No breakage occurred when a force of 500 N was applied. The tablets could not be comminuted using a hammer, nor with the assistance of a pestle and mortar.

In vitro release of the active ingredient from the tablets was determined in a paddle stirrer apparatus with sinker in accordance with Pharm. Eur.. The temperature of the release medium was 37°C and the rotational speed of the stirrer 75 min^{-1}. The release medium used was 600 ml of intestinal juice, pH 6.8. The quantity of active ingredient released in each case into the dissolution medium at any one time was determined by spectrophotometry.

Time	Quantity of active ingredient released
30 min	20%
240 min	43%
480 min	83%
720 min	90%

Example 2

Powder mixture	Complete batch	Per tablet
Tramadol HCl	100.1 g	100 mg
Polyethylene oxide MW 5000 000 (Polyox WSR Coagulant, from Dow),	300.0 g	299.7 mg
Hydroxypropylmethylcellulose (Hypromellose 100 000 mPa)	50.05 g	50.0 mg
Butylhydroxytoluene (BHT)	0.25 g	0.25 mg
Foam Hydroxypropylmethylcellulose (Hypromellose 100 000 mPa)	0.250 g	0.25 mg
Dist. water	49.8 g	

The powder mixture was first produced as stated in Example 1.

The foam was produced by dissolving the stated quantity of Hypromellose in distilled water. A foam was then produced using a high performance homogeniser (IKA Ultraturrax 25 Basic) by stirring initially for 2 minutes at level 1, then for 2 minutes with a mixer/granulator at level 2 and finally for 3 minutes at level 3. The powder mixture was slowly added to the foam with constant stirring in a mixer (Kenwood Major Classic 25 Basic).

The granulated mixture was then dried for 24 hours at 40°C and, after being passed through a screen (from Frewitt, model GLA-A-ORV) with 1 mm orifices, was press-moulded into tablets with a weight of 450.2 mg. A model EK 0 eccentric press with a round tabletting tool having a diameter of 10 mm and a radius of curvature of 8 mm was used for this purpose. These tablets were dried for 1 hour at 70°C.

The breaking strength of the tablets was determined using the above-stated method. No breakage occurred when a force of 500 N was applied. The tablet could not be comminuted using a hammer, nor with the assistance of a pestle and mortar.

In vitro release of the active ingredient from the tablets was determined in a paddle stirrer apparatus with sinker in accordance with Pharm. Eur.. The temperature of the release medium was 37°C and the rotational speed of the stirrer 75 min^{-1}. The release medium used was 600 ml of intestinal juice, pH 6.8. The quantity of active ingredient released in each case into the dissolution medium at any one time was determined by spectrophotometry.

Time	Quantity of active ingredient released
30 min	12%
240 min	47%
480 min	71%
720 min	84%

Claims

1. A process for the production of a solid dosage form with at least reduced potential for abuse, characterised in that

a) there is added to a formulation mixture containing at least one active ingredient with potential for abuse (A) and at least one synthetic or natural polymer (C), which exhibits a breaking strength of at least 500 N, a solvent for the polymer (C) at least in quantities such that the formulation mixture is uniformly moistened
b) the composition which has been at least moistened in this manner is optionally divided into sub-portions,
c) the portion(s) are dried and
d) shaped to yield the dosage form,

polymer (C) being used in quantities such that the dosage form also has a minimum breaking strength of at least 500 N.

2. A process according to claim 1, characterised in that the dried sub-portions in each case correspond to the mass of a unit of the dosage form.

3. A process according to claim 1 or claim 2, characterised in that, before addition of the solvent, the formulation mixture is already dispersed in a liquid dispersant in which the polymer component (C) is not soluble.

4. A process according to claim 3, characterised in that, before or after the formulation composition is dispersed, it is already divided into sub-portions in each case corresponding to the mass of a unit of the dosage form.

5. A process according to claim 3 or claim 4, characterised in that the solvent and the dispersant are miscible with one another.

6. A process according to claim 1, characterised in that the solvent is incorporated into the formulation mixture as a foam.

7. A process according to claim 6, characterised in that the foam is stabilised with the assistance of foam stabilisers.

8. A process according to claim 6 or claim 7, characterised in that the composition granulated with the solvent foam is dried.

9. A process according to claim 8, characterised in that the dried, granulated composition is divided into sub-portions, which in each case correspond to the mass of a unit of the dosage form, and shaped to yield the dosage form.

10. A process according to claim 1, characterised in that solvent is added to the formulation mixture in an amount such that a shapeable paste is obtained.

11. A process according to claim 10, characterised in that, before of after it is dried, the paste is divided into sub-portions and the dried portions, optionally after being further divided in each case into a portion corresponding to the mass of a unit of the dosage form, are shaped or converted into the dosage form.

12. A process according to claim 11, characterised in that the sub-portions have the form of strands.

13. A process according to claim 12, characterised in that the strands are produced with the assistance of a screen or a strand former.

14. A process according to claim 12, characterised in that the dried strands are singulated and shaped to yield the dosage form.

15. A process according to claim 14, characterised in that shaping proceeds with the assistance of a tablet press.

16. A process according to claim 12, characterised in that the dried strands are shaped with the assistance of shaping rollers or shaping belts equipped with rollers to yield the dosage form.

17. A process according to claim 11, characterised in that the paste is converted into a planar structure, from which the dosage form is stamped.

18. A process according to claims 10 to 12, characterised in that the process is performed with the assistance of an extruder.

19. A process according to claim 1, characterised in that solvent is added to the formulation mixture in a quantity such that at least the polymer component (C) is dissolved.

20. A process according to claim 19, characterised in that the solution is converted into a planar structure.

21. A process according to claim 20, characterised in that the planar structure is obtained with the assistance of an extruder with a flat die or by casting the solution onto a level planar support.

22. A process according to claims 19 to 21, characterised in that the dosage form is shaped by stamping from the dried planar structure or obtained by calendering.

23. A process according to claim 19, characterised in that the solution is divided into portions such that, after drying, they correspond in each case to the mass of a unit of the dosage form.

24. A process according to claim 23, characterised in that the portions are placed in moulds corresponding to the shape of a unit of the dosage form.

25. A process according to claim 19, characterised in that the solution is divided into any desired portions, which, after drying, are optionally recombined, and shaped to yield the dosage form.

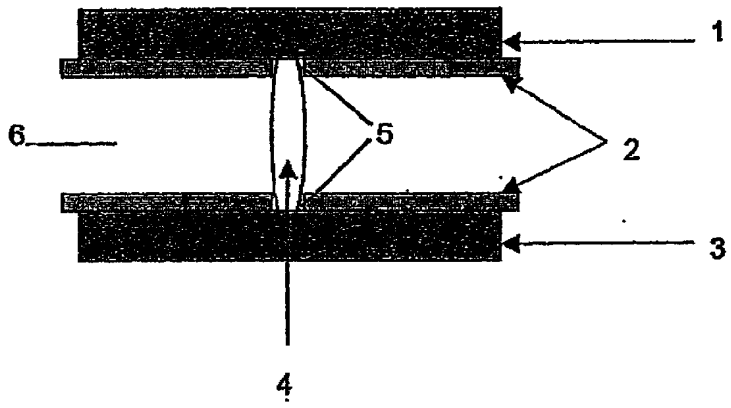
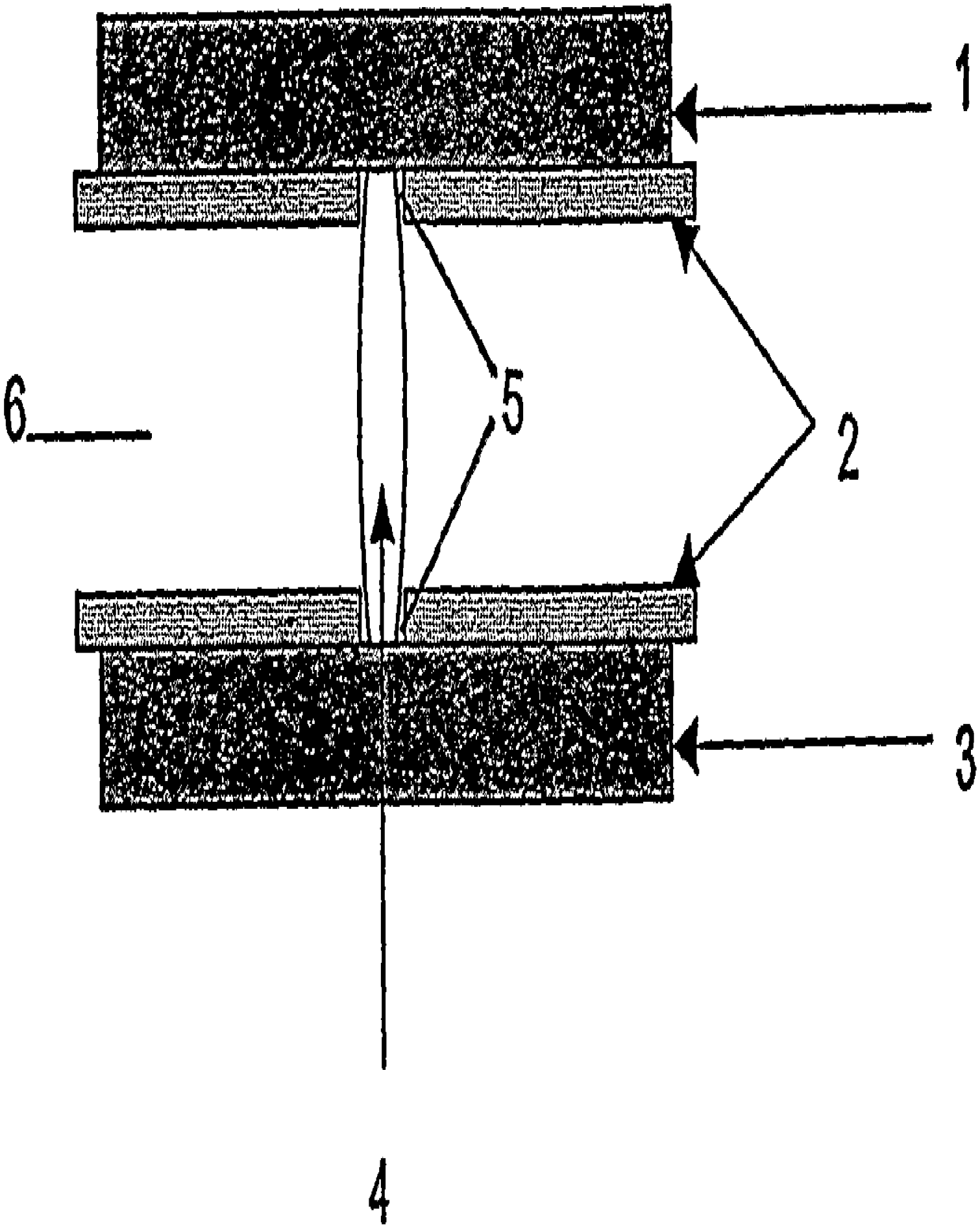


FIGURE 1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